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Jennifer Grasser

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=> s copolymer(l)(lactic acid or glycolic acid)

         93698 COPOLYMER
           227 COPOLYMERS
         93812 COPOLYMER
                 (COPOLYMER OR COPOLYMERS)
          2051 LACTIC
       4599356 ACID
          7305 ACIDS
       4604710 ACID
                 (ACID OR ACIDS)
          1936 LACTIC ACID
                 (LACTIC(W)ACID)
          2458 GLYCOLIC
       4599356 ACID
          7305 ACIDS
       4604710 ACID
                 (ACID OR ACIDS)
          2435 GLYCOLIC ACID
                 (GLYCOLIC(W)ACID)
L1         255 COPOLYMER(L)(LACTIC ACID OR GLYCOLIC ACID)

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=> s copolymer(l)(lactic acid or glycolic acid) or l1

L2 756 FILE MEDLINE
L3 2380 FILE CAPLUS
L4 223 FILE BIOSIS
L5 1764 FILE EMBASE
L6 764 FILE WPIDS

TOTAL FOR ALL FILES
L7 5887 COPOLYMER(L)(LACTIC ACID OR GLYCOLIC ACID) OR L1

=> s l7 and pertuss?

L8 1 FILE MEDLINE
L9 4 FILE CAPLUS
L10 0 FILE BIOSIS
L11 9 FILE EMBASE
L12 1 FILE WPIDS

TOTAL FOR ALL FILES
L13 15 L7 AND PERTUSS?

=> dup rem l13

PROCESSING COMPLETED FOR L13
L14 15 DUP REM L13 (0 DUPLICATES REMOVED)

=> s l7 and (ptd or filmentous hemaglutinin or fha or pertactin or fimbrae)

L15 0 FILE MEDLINE
L16 2 FILE CAPLUS
L17 0 FILE BIOSIS
L18 0 FILE EMBASE
L19 0 FILE WPIDS

TOTAL FOR ALL FILES
L20 2 L7 AND (PTD OR FILMENTOUS HEMAGLUTININ OR FHA OR PERTACTIN OR FIMBRAE)

=> s l20 or l13

L21 1 FILE MEDLINE
L22 4 FILE CAPLUS
L23 0 FILE BIOSIS
L24 9 FILE EMBASE
L25 1 FILE WPIDS

TOTAL FOR ALL FILES
L26 15 L20 OR L13

=> s l26 and vaccin?

L27 1 FILE MEDLINE
L28 3 FILE CAPLUS
L29 0 FILE BIOSIS
L30 7 FILE EMBASE

L31 1 FILE WPIDS

TOTAL FOR ALL FILES
L32 12 L26 AND VACCIN?

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PROCESSING COMPLETED FOR L32
L33 12 DUP REM L32 (0 DUPLICATES REMOVED)

=> d cbib abs 1-12

applicant

L33 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2000 ACS
2000:161163 Document No. 132:199032 Method for inducing a cell-mediated immune response and parenteral **vaccine** formulations therefor. Brayden, David James (Elan Corporation, PLC, Ire.). PCT Int. Appl. WO 2000012125 A1 20000309, 68 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-IE87 19990831. PRIORITY: US 1998-PV98760 19980901.
AB A method of inducing either a TH1 polarized immune response, a TH2 polarized immune response, or a combined TH1 and TH2 response to an antigen, and assocd. **vaccine** formulations, are disclosed. A method is provided for inducing a polarized TH1 response by parenteral administration of microparticles sized such that at least 50% of the microparticles are less than 5 .mu.m, the microparticles contg. antigen entrapped or encapsulated by a biodegradable polymer. Addnl., a method is provided for inducing a polarized TH2 response by parenteral administration of nanoparticles sized such that at least 50% of the nanoparticles are less than 600 nm, the nanoparticles contg. antigen entrapped or encapsulated by a biodegradable polymer. **Vaccine** formulations contg. the B. **pertussis** antigens **PTd**, **FHA**, or a combination of **PTd** and **FHA**, are provided.

applicant

L33 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2000 ACS
2000:161162 Document No. 132:199031 Oral **vaccine** compositions. Brayden, David James (Elan Corporation, PLC, Ire.). PCT Int. Appl. WO 2000012124 A1 20000309, 52 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-IE86 19990831. PRIORITY: US 1998-98759 19980901.
AB Oral **vaccine** formulations are disclosed having microparticles sized such that at least 50% of the microparticles are less than 5 .mu.m, preferably less than 3 .mu.m, the microparticles contg. antigen entrapped

or encapsulated, e.g. by a solvent evapn. method, by a biodegradable polymer, e.g. poly(D,L-lactide-co-glycolide). Addnl., oral **vaccine** formulations are disclosed having nanoparticles sized such that at least 50% of the microparticles are less than 600 nm, preferably less than 500 nm, the nanoparticles contg. antigen entrapped or encapsulated, e.g. by a coacervation method, by a biodegradable polymer, e.g. poly(D,L-lactide-co-glycolide). Protective **vaccine** formulations contg. the B. **pertussis** antigens **PTd** or a combination of **PTd** and **FHA** are provided.

L33 ANSWER 3 OF 12 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1999186488 EMBASE Single-administration **vaccines**:
Controlled-release technology to mimic repeated immunizations. Cleland J.L.. J.L. Cleland, Pharmaceutical R and D, Genentech, 1 DNA Way, South San Francisco, CA 94080, United States. cleland@gene.com. Trends in Biotechnology 17/1 (25-29) 1999.
Refs: 33.
ISSN: 0167-7799. CODEN: TRBIDM.
Publisher Ident.: S 0167-7799(98)01272-4. Pub. Country: United Kingdom.
Language: English. Summary Language: English.
AB The most effective mechanism for the elimination of disease from society is the use of **vaccinations**, but these often require repeated administration. However, single-administration **vaccine** formulations provide the repeated administrations automatically. One approach is the development of injectable controlled-release microsphere formulations containing the **vaccine** antigen that is released as a pulse 1-6 months after injection. The time of the pulse is dependent upon the rate of polymer degradation, which is dictated by the polymer's composition and molecular weight. This controlled-release technology may provide complete protection against disease after a single administration.

L33 ANSWER 4 OF 12 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1999016458 EMBASE Approaches to new **vaccines**. Mahon B.P.; Moore A.; Johnson P.A.; Mills K.H.G.. B.P. Mahon, Infection and Immunity Group, National University of Ireland, Maynooth, County Kildare, Ireland.
Critical Reviews in Biotechnology 18/4 (257-282) 1998.
Refs: 161.
ISSN: 0738-8551. CODEN: CRBTE5. Pub. Country: United States. Language: English. Summary Language: English.
AB The explosive technological advances in the fields of immunology and molecular biology in the last 5 years had an enormous impact on the identification of candidate **vaccines** against diseases, which until a few years ago seemed uncontrollable. Increased knowledge of the immune system has helped to define the mechanisms that underlie successful immunization and is now being exploited to develop improved versions of existing **vaccines** and new **vaccines** against emerging pathogens, tumors, or autoimmune diseases. An understanding of the mechanisms of action of novel adjuvants and the development of new vector and delivery systems will have a major impact on **vaccine** strategies. The use of DNA encoding antigens from pathogenic viruses, bacteria, and parasites as **vaccines** is a new approach that is receiving considerable attention. This and other innovative approaches, including **vaccine** production in plants, are appraised in this review. The successful eradication of smallpox and the imminent eradication of poliomyelitis by worldwide immunization campaigns provide positive examples of how the **vaccine**-mediated approach can lead to disease elimination; with the advent of new **vaccines** and improved delivery systems, there is no scientific reason why these

successes cannot be repeated.

L33 ANSWER 5 OF 12 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1998131448 EMBASE Towards a multipurpose mucosal **vaccination** using phosphorylcholine as a unique antigen?. Trolle S.; Andremont A.; Fattal E.. E. Fattal, Lab. Physic. Pharmacotech. Biopharm., URA-CNRS 1218, Faculte de Pharmacie, 92296 Chatenay-Malabry Cedex, France. S.T.P. Pharma Sciences 8/1 (19-30) 1998.
Refs: 112.
ISSN: 1157-1489. CODEN: STSSE5. Pub. Country: France. Language: English. Summary Language: French.
AB Intestinal and pulmonary bacterial infections are a major cause of worldwide child mortality. The development of a sole plurispecific **vaccine** against those infections is a World Health Organization priority. In that respect, we hypothesized that immunization with phosphorylcholine, a ubiquitous antigen present on different pathogenic microorganisms, might be an original approach. Our **vaccine** is constituted of phosphorylcholine coupled to a protein carrier and entrapped in biodegradable microspheres. This **vaccine** is stable and adequate for oral or intranasal immunization and thus for the stimulation of the common mucosal immune system. **Vaccinated** animals were statistically protected against either a lethal oral challenge by Salmonella typhimurium, or a lethal nasal challenge by Streptococcus pneumoniae. The results constitute a strong impetus to explore the potentialities of our candidate **vaccine**.

L33 ANSWER 6 OF 12 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1998036607 EMBASE Conference Science Medal 1997 lecture at British Pharmaceutical Conference, Scarborough, United Kingdom, September 15-18, 1997: Recent advances in **vaccine** adjuvants for systemic and mucosal administration. O'Hagan D.T.. D.T. O'Hagan, Chiron Corporation, 4560 Horton Street, Emeryville, CA 947608, United States. Journal of Pharmacy and Pharmacology 50/1 (1-10) 1998.
Refs: 57.
ISSN: 0022-3573. CODEN: JPPMAB. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB Although **vaccines** produced by recombinant DNA technology are safer than traditional **vaccines**, which are based on attenuated or inactivated bacteria or viruses, they are often poorly immunogenic. Therefore, adjuvants are often required to enhance the immunogenicity of these **vaccines**. A number of adjuvants which are particulates of defined dimensions (< 5 .mu.m) have been shown to be effective in enhancing the immunogenicity of weak antigens in animal models. Two novel adjuvants which possess significant potential for the development of new **vaccines** include an oil-in-water microemulsion (MF59) and polymeric microparticles. MF59 has been shown to be a potent and safe adjuvant in human subjects with several **vaccines** (for example HSV-2, HIV-1 and influenza virus). An MF59 adjuvanted influenza has been recommended for approval in Italy. Microparticles prepared from the biode gradable polymers the poly(lactide-co-glycolides) (PLG) are currently undergoing extensive pre-clinical evaluation as **vaccine** adjuvants. Because of their controlled release characteristics, microparticles also possess considerable potential for the development of single dose **vaccines**. The development of single dose **vaccines** would offer significant advantages and would improve **vaccination** uptake rates in at risk populations, particularly in the developing world. In addition to systemic administration, microparticles have also also been shown to enhance the immunogenicity of **vaccines** when administered by mucosal routes. Therefore microparticles may allow the development of novel **vaccines** which can be administered by non-parenteral routes. Mucosal administration of

vaccines would significantly improve patient compliance by allowing immunization to be achieved without the use of needles. An alternative approach to the development of mucosally administered **vaccines** involves the production of genetically detoxified toxins. Heat labile enterotoxin (LT) from Escherichia coli and cholera toxin from Vibrio cholerae are two closely related bacterially produced toxins, which are the most potent adjuvants available. However, these molecules are too toxic to be used in the development of human **vaccines**. Nevertheless, these toxins have been modified by site-directed mutagenesis to produce molecules which are adjuvant active, but non-toxic. The most advanced of these molecules (LTK63), which has a single amino acid substitution in the enzymatically active subunit of LT, is active as an adjuvant, but non-toxic in pre-clinical models. The approach of genetically detoxifying bacterial toxins to produce novel adjuvants offers significant potential for the future development of mucosally administered **vaccines**.

L33 ANSWER 7 OF 12 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1998073457 EMBASE Awakening the global conscience: Who will benefit from new **vaccines** in the 21st century?. Nossal G.J.V.. G.J.V. Nossal, Department of Pathology, University of Melbourne, Parkville, Vic. 3052, Australia. Immunology and Cell Biology 75/6 (584-586) 1997. ISSN: 0818-9641. CODEN: ICBIEZ. Pub. Country: Australia. Language: English. Summary Language: English.

AB The World Health Organization's (WHO) Global Programme for **Vaccines** and Immunization has three linked aims. The first is to give the so-called Expanded Programme on Immunization (EPI) **vaccines** to as many of the 125 million children who are born into the world each year as possible. The second is to ensure for the word an adequate supply of **vaccines**, and to safeguard **vaccine** quality. The third is in the field of **vaccine** research and development, not only coordinating the worldwide effort for new and improved **vaccines** but also preparing the way for their introduction into the EPI and continually to seek ways to simplify **vaccination** schedules. Enormous effort has gone into the polio eradication campaign. Following brilliant progress in both India and Africa, the goal of eradication by the year 2000 or shortly thereafter now seems achievable. Although a decision has not yet been taken, an attempt at measles eradication may well be the next huge challenge. The Global Programme for **Vaccines** and Immunization (GPV) is closely tied up with the Children's **Vaccine** Initiative (CVI) which is the name given to an umbrella organization which seeks to unite all the forces in the world promoting widespread use of **vaccines**. The chief functions of CVI are to be a strategic think tank, particularly as regards priorities; and to be a strong, consistent and effective advocacy group. Previously there had been some misunderstanding of the respective roles of WHO and CVI. These have now been cleared up by a dual stratagem - one single person, Dr JW Lee, as the administrative head of both Programmes; and one single Scientific Advisory Group of Experts or SAGE to guide the scientific aspects of both Programmes. The author has the honour of being Chairman of SAGE. It is apparent, however, that resource constraints are looming large in the affairs of both GPV and CVI. Clearly, the newer **vaccines** will be more expensive than the traditional ones, and the world must grope for new mechanisms to bring the fruits of the current

upsurge of interest in **vaccine** development to all the countries of the world, not just the affluent ones.

L33 ANSWER 8 OF 12 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
96029413 EMBASE Document No.: 1996029413. Orally administered microencapsulated Bordetella **pertussis** fimbriae protect mice from B. **pertussis** respiratory infection. Jones D.H.; McBride B.W.; Thornton C.; O'Hagan D.T.; Robinson A.; Farrar G.H.. Experimental Vaccines Section, Microbial Antigens Department, Applied Microbiology/Research Centre, Porton Down,Salisbury, Wiltshire SP4 0JG, United Kingdom. Infection and Immunity 64/2 (489-494) 1996. ISSN: 0019-9567. CODEN: INFIBR. Pub. Country: United States. Language: English. Summary Language: English.

AB Fimbriae from Bordetella **pertussis** have been encapsulated in poly(lactide- co-glycolide) microparticles of a size appropriate for uptake by the immune inductive tissues of the gastrointestinal tract. Mice were immunized by oral gavage with a single dose of 10 .mu.g of microencapsulated fimbriae. The resulting immune responses were compared with those resulting from intraperitoneal injection of mice with equivalent amounts of fimbriae adsorbed onto alhydrogel. The examination of serum and mucosal secretions, collected over a 6-week period, for specific antifimbrial antibodies clearly demonstrated that only orally immunized animals mounted measurable immune responses in external secretions. Six weeks after immunization, all immunized animals were protected against intranasal challenge with live B. **pertussis**.

L33 ANSWER 9 OF 12 MEDLINE
96351451 Document Number: 96351451. Poly(lactide-co-glycolide) microencapsulation of **vaccine** antigens. Jones D H; McBride B W; Farrar G H. (Microbial Antigens Department, Centre for Applied Microbiology and Research, Salisbury, Wilts, UK.) JOURNAL OF BIOTECHNOLOGY, (1996 Jan 26) 44 (1-3) 29-36. Journal code: AL6. ISSN: 0168-1656. Pub. country: Netherlands. Language: English.

AB Fimbriae from Bordetella **pertussis** have been encapsulated in poly(lactide-co-glycolide) (PLG) microspheres of a size appropriate for oral administration. The binding of antibodies which react with conformational or linear fimbrial epitopes, to fimbriae released from microspheres, suggested that the process of was not detrimental to the native integrity of the protein. Mice were immunised by oral gavage with a single dose of microencapsulated fimbriae, or with fimbriae adsorbed onto alhydrogel and administered by intraperitoneal injection. The resulting immune responses in serum were comparable but only oral administration of microencapsulated fimbriae elicited specific immune responses in external secretions. Six weeks after immunisation, both groups of immunised animals were protected against challenge with live B. **pertussis**.

L33 ANSWER 10 OF 12 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
95187896 EMBASE Document No.: 1995187896. Protection of mice from Bordetella **pertussis** respiratory infection using microencapsulated **pertussis** fimbriae. Jones D.H.; McBride B.W.; Jeffery H.; O'Hagan D.T.; Robinson A.; Farrar G.H.. Experimental Vaccines Section, Microbial Antigens Department, Research Division,Porton Down, Salisbury SP4 0JG, United Kingdom. Vaccine 13/7 (675-681) 1995. ISSN: 0264-410X. CODEN: VACCDE. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Conditions have been established which allow the efficient entrapment of Bordetella **pertussis** fimbriae in poly(lactide-co-glycolide) microspheres. Fimbriae released from the matrix were found to have

retained some degree of conformational structure as determined by assessing the capacity of fimbrial protein to bind to antibodies mapping to either conformational or denatured structures on the fimbriae. Following a single intraperitoneal injection equivalent amounts of fimbriae either encapsulated in microspheres with a mean diameter of 24 .mu.m and an estimated in vitro protein release rate of approximately 42 days, or conventionally adjuvanted with alhydrogel, elicited vigorous immune responses in mice. The encapsulated fimbriae appear to elicit marginally lower serum antibody levels than those induced by equivalent amounts of alhydrogel-adjuvanted fimbriae. Mice immunised with both preparations were, however, protected against intranasal infection with live B. **pertussis** as evidenced by the significant reduction in levels of bacterial colonisation observed in the lungs and tracheas of immunised animals when compared to the immunologically naive controls.

L33 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2000 ACS
1993:525196 Document No. 119:125196 Biodegradable polyester of 4-hydroxyproline and pharmaceutical composition containing the same. Mochizuki, Seiji; Nawata, Kiyoshi; Makino, Yuji; Suzuki, Yoshiki (Teijin Ltd., Japan). Eur. Pat. Appl. EP 531091 A1 19930310, 25 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, IE, IT, LI, NL, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1992-307924 19920901. PRIORITY: JP 1991-254290 19910906.
AB A biodegradable **copolymer** comprising a 4-hydroxyproline deriv. and an aliph. .alpha.-hydroxycarboxylic acid is prepd. as a drug carrier to control drug release by suppressing the initial burst phenomenon. For example, trans-4-hydroxy-L-proline/**glycolic acid** **copolymer** was prepd. and insulin microcapsules contg. the **copolymer** was formulated.

L33 ANSWER 12 OF 12 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1988-121200 [18] WPIDS
CR 1989-272277 [38]; 1996-189757 [20]; 1998-530832 [45]; 1998-541706 [46]; 1998-567595 [48]; 1999-094826 [08]
AB EP 266119 A UPAB: 19991026 x after July
Compsn. to be orally administered to animals and capable of delivering a bioactive agent (I) to the Peyer's patch of the animal comprises (I) encapsulated in a biodegradable and biocompatible excipient to form microcapsules of a size capable of being taken up by the Peyer's patch and capable of passing through the gastrointestinal tract without degradation.
Pref. the excipient is selected from poly(**glycolic acid**), **copolymers** of mixed DL-lactide and glycolide, copolyoxalates, polycaprolactone, poly(lactide-co-caprolactone), poly(esteramides), polyorthoesters and poly(beta-hydroxybutyric acid). The microcapsules are pref. of 3 micron or less in dia. (I) may be a protozoal, viral, fungal or bacterial antigen e.g. trinitrophenyl keyhole limpet hemocyanin or a toxoid e.g. of a staphylococcal enterotoxin.
USE/ADVANTAGE - Use of the compsn. results in (I) reaching and being taken up by the Peyer's patch and thereby stimulating the mucosal immune system. The compsn. can be used with antigens to **vaccinate** against viral, bacterial, protozoan or fungal diseases e.g influenza, respiratory syncytial, parainfluenza viruses, Hemophilus influenzae, Bordetella **pertussis**, Neisseria gonorrhea, Streptococcus pneumoniae and Plasmodium falciparum.
Dwg.0/0
ABEQ EP 266119 B UPAB: 19940831
An oral composition to be administered to animals, including humans, and

capable of delivering a bioactive agent to the Peyer's patch of said animal, comprising an effective amount of the bioactive agent encapsulated in a biodegradable, biocompatible excipient so as to form microcapsules having a size less than or equal to 1 micro m, being capable of being taken up selectively by the Peyer's patch and capable of passing through the gastrointestinal tract without degradation.
Dwg.0/0

=> s l7 and oral administ? and vaccin?

L34	1	FILE MEDLINE
L35	3	FILE CAPLUS
L36	0	FILE BIOSIS
L37	12	FILE EMBASE
L38	3	FILE WPIDS

TOTAL FOR ALL FILES
L39 19 L7 AND ORAL ADMINIST? AND VACCIN?

=> s l39 not l32

L40	0	FILE MEDLINE
L41	3	FILE CAPLUS
L42	0	FILE BIOSIS
L43	12	FILE EMBASE
L44	2	FILE WPIDS

TOTAL FOR ALL FILES
L45 17 L39 NOT L32

=> dup rem 145

PROCESSING COMPLETED FOR L45
L46 17 DUP REM L45 (0 DUPLICATES REMOVED)

=> d cbib abs 1-17

L46 ANSWER 1 OF 17 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
2000001043 EMBASE Oral tolerance elicited in mice by .beta.-lactoglobulin entrapped in biodegradable microspheres. Pecquet S.; Leo E.; Fritsche R.; Pfeifer A.; Couvreur P.; Fattal E.. S. Pecquet, Food Immunology, Nestec SA, Nestle Research Center Lausanne, BP 44, ~~CH-1000 Lausanne 26,~~ Switzerland. sophie.pecquet@rdls.nestle.com. Vaccine 18/13 (1196-1202) 2000.
Refs: 39.
ISSN: 0264-410X. CODEN: VACCDE.
Publisher Ident.: S 0264-410X(99)00384-9. Pub. Country: United Kingdom.
Language: English. Summary Language: English.
AB **Oral administration** of antigen is known to be appropriate for some **vaccine** purposes as well as oral tolerance induction. In the present study, **oral administration** of .beta.-lactoglobulin (BLG) loaded poly(D,L-lactide-co- glycolide) (D,L-PLG) microspheres induced tolerance was evaluated. A single feeding of 5 .mu.g of encapsulated BLG tolerised BALB/c mice to subsequent BLG parenteral challenge, suppressing the specific humoral, intestinal and cellular responses. The tolerogenic efficient dose was then reduced 10,000 times, compared to **oral administration** of soluble BLG.

This suggests that loading food proteins into D,L-PLG microspheres might be a potential tool for inducing oral tolerance with allergens.

L46 ANSWER 2 OF 17 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
2000064382 EMBASE Oral DNA **vaccination** promotes mucosal and systemic immune responses to HIV envelope glycoprotein. Kaneko H.; Bednarek I.; Wierzbicki A.; Kiszka I.; Dmochowski M.; Wasik T.J.; Kaneko Y.; Kozbor D.. D. Kozbor, Dept. of Microbiology and Immunology, Thomas Jefferson University, 1020 Locust Street, Philadelphia, PA 19107-6799, United States. Virology 267/1 (8-16) 1 Feb 2000.
Refs: 32.
ISSN: 0042-6822. CODEN: VIRLAX. Pub. Country: United States. Language: English. Summary Language: English.
AB In this report, we described induction of HIV envelope (env)-specific systemic and mucosal immune responses by oral **vaccination** of BALB/c mice with env-encoded plasmid DNA encapsulated in poly(DL-lactide-co-glycolide) (PLG) microparticles. We demonstrated that intragastric administration of the encapsulated plasmid DNA resulted in transduced expression of the env glycoprotein in the intestinal epithelium. Mice immunized orally exhibited env-specific type 1 and cytotoxic T lymphocyte (CTL) responses in spleen and the inductive (Peyer's patches) and effector (lamina propria) mucosal tissues of gut. **Oral administration** of PLG-encapsulated plasmid DNA encoding gp160 also induced env-specific serum antibodies, and an increased level of IgA directed to gp160 was detected in fecal washes of the immunized mice. In contrast, intramuscular (i.m.) administration of naked or PLG-encapsulated DNA **vaccine** induced only systemic cellular and humoral responses to the env glycoprotein. Using an HIV env-expressing recombinant **vaccinia** viral intrarectal murine challenge system, we observed higher resistance to mucosal viral transmission in mice immunized orally than in animals injected i.m. with PLG-encapsulated plasmid DNA encoding gp160. Results of these studies demonstrate the feasibility of using orally delivered PLG microparticles containing plasmid DNA-encoded HIV gp160 for induction of env-specific systemic and mucosal immune responses and protection against recombinant HIV env **vaccinia** virus challenge. (C) 2000 Academic Press.

L46 ANSWER 3 OF 17 CAPLUS COPYRIGHT 2000 ACS
1999:147767 Document No. 130:242309 Microspherical carriers for transporting oral **vaccines** to lymph tissues in birds. Hoshi, Sumio; Uchino, Akemi; Kusanagi, Koichi; Ihara, Takeshi; Ueda, Susumu (Nippon Seibutsu Kagaku Kenkyusho, Japan). Jpn. Kokai Tokkyo Koho JP 11060506 A2 19990302 Heisei, 5 pp. (Japanese). CODEN: JKXXAF. APPLICATION: JP 1997-226577 19970822.
AB **Lactic acid-glycolic acid copolymer** having mol. wt. 4 X 104 - 12 X 104 is made into microspheres [as carriers having particle size .ltoreq. 10 .mu.m] for transporting **vaccines** [antigens] to duct lymph tissues in birds after **oral administration**.

L46 ANSWER 4 OF 17 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1999-302625 [25] WPIDS
AB WO 9920253 A UPAB: 19990630
NOVELTY - Encapsulating an active substance in a biodegradable polymer comprises:
(a) dissolving the polymer in an organic solvent;
(b) (i) dispersing the active substance in, or (ii) emulsifying the active substance in water or an aqueous solvent with, the solution from (a) to give a dispersion or an emulsion respectively with the active substance as the inner phase;

(c) encapsulating the product from (b) using an aqueous polyethylene glycol solution as a continuous phase to give micro- or nanoparticles.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for sustained release micro- or nano-particles prepared by the above process.

USE - For encapsulating soluble and highly insoluble active substances e.g. drugs, peptides, pesticides, fragrances, flavoring agents, catalysts or herbicides to allow sustained release.

ADVANTAGE - The process allows high incorporation efficiency and/or gives smaller microparticles and even nanoparticles containing highly active doses of agent. The amount of organic solvent and energy required is reduced compared to prior art processes. The process also avoids the use of PVA or other surfactants.

L46 ANSWER 5 OF 17 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

1999242100 EMBASE PLG microparticles stabilised using enteric coating polymers as oral **vaccine** delivery systems. Delgado A.; Lavelle E.C.; Hartshorne M.; Davis S.S.. S.S. Davis, Dept. of Pharmaceutical Sciences, University of Nottingham, University Park, Nottingham NG7 2RD, United Kingdom. Stanley.Davis@nottingham.ac.uk. Vaccine 17/22 (2927-2938)

16 Jul 1999.

Refs: 33.

ISSN: 0264-410X. CODEN: VACCDE.

Publisher Ident.: S 0264-410X(99)00140-1. Pub. Country: United Kingdom.

Language: English. Summary Language: English.

AB Novel poly(dl-lactide-co-glycolide) microparticles for oral **vaccine** delivery were formulated using the enteric polymers Eudragit.RTM. L100-55 and carboxymethylethylcellulose (CMEC) as stabilisers. To serve as a control, microparticles were also produced using the conventional PVA surfactant. In all three cases the antigen, ovalbumin (OVA)-loaded microparticles produced were less than 5 .mu.m in diameter and had a spherical, smooth rounded appearance. The presence of surfactants at the microparticle surface was demonstrated by the surface analysis techniques, XPS and SSIMS. Incubation of microparticles with solutions of pepsin or trypsin led to the removal of a proportion of the antigen associated with all three systems. However, in three CMEC-stabilised microparticle formulations and one of three Eudragit formulations, a high percentage of the associated antigen was protected from removal by a solution of pepsin at pH 1.2 compared with the PVA-stabilised microparticles. In addition, with certain CMEC and Eudragit formulations a degree of protection was also afforded to the associated OVA against removal by trypsin at pH 7.4. Following the incubation of microparticles in simulated gastric fluid a higher percentage of intact antigenic OVA was detected in microparticles stabilised using CMEC than in the PVA- and Eudragit- stabilised formulations. Oral immunisation of mice with OVA-loaded microparticles stabilised using either of the three surfactants led to the induction of specific serum IgG and salivary IgA antibodies. Significantly higher levels of specific salivary IgA antibody to OVA were measured in mice immunised with the CMEC-stabilised microparticles than with the other two formulations. This novel approach in PLG microparticle formulation may have potential in increasing the efficacy of microparticulate systems for the **oral administration** of **vaccines**.

L46 ANSWER 6 OF 17 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

1999152557 EMBASE Single-dose mucosal immunization with biodegradable microparticles containing a Schistosoma mansoni antigen. Baras B.; Benoit M.-A.; Dupre L.; Poulain-Godefroy O.; Schacht A.-M.; Capron A.; Gillard

J.; Riveau G.. B. Baras, Lab. des Relations Hotes-Parasite, Strategies Vaccinales, Institut Pasteur de Lille, 1 rue du Professeur Calmette, F-59019 Lille Cedex, France. ipv@pasteur-lille.fr. Infection and Immunity 67/5 (2643-2648) 1999.
Refs: 30.
ISSN: 0019-9567. CODEN: INFIBR. Pub. Country: United States. Language: English. Summary Language: English.

AB The purpose of this work was to assess the immunogenicity of a single nasal or **oral administration** of recombinant 28-kDa glutathione S-transferase of Schistosoma mansoni (rSm28GST) entrapped by poly(lactide-co-glycolide) (PLG)- or polycaprolactone (PCL)-biodegradable microparticles. Whatever the polymer and the route of administration used, the equivalent of 100 .mu.g of entrapped rSm28GST induced a long-lasting and stable antigen-specific serum antibody response, with a peak at 9 to 10 weeks following immunization. Isotype profiles were comparable, with immunoglobulin G1 being the predominant isotype produced. The abilities of specific antisera to neutralize the rSm28GST enzymatic activity have been used as criteria of immune response quality. Pooled 10-week sera from mice receiving PLG microparticles by the nasal or oral route neutralized the rSm28GST enzymatic activity, whereas sera of mice receiving either PCL microparticles, free rSm28GST, or empty microparticles inefficiently neutralized this enzymatic activity. Finally, this study shows that a single administration of these microparticles could provide distinct and timely release pulses of microencapsulated antigen, which might greatly facilitate future **vaccine** development.

L46 ANSWER 7 OF 17 CAPLUS COPYRIGHT 2000 ACS
1999:252940 Document No. 131:72403 Preparation of oral microspheres carrying Vivrio cholera **vaccine** and its target's distribution. Zhang, Wenbin; Jia, Wenxiang; Liu, Cong; Zhang, Zairong; Liu, Li; Deng, Xianmo; Li, Xionwei; Xiong, Chengdong; Meng, Li; Zheng, Zhanxi (School of Basic Medical Sciences, WCUMS, Chengdu, 610041, Peop. Rep. China). Huaxi Yike Daxue Xuebao, 30(1), 31-33 (Chinese) 1999. CODEN: HYDXET. ISSN: 0257-7712. Publisher: Huaxi Yike Daxue.

AB To prep. oral biodegradable microspheres carrying V. cholera **vaccine**, the major outer membrane protein (OMP, MW=41kd) as a common antigen of cholera Vibriae was obtained from the classical strain Inaba 569 B, and the OMP was encapsulated in the biodegradable delivery system comprising Poly (DL-Lactide)-Co-Poly (ethylene glycol) microspheres. The av. size of the microspheres was less than 5.mu.m, the amt. of OMP encapsulated in microspheres was 15.3%. It was found that microspheres were taken up in Peyer's patches and then distributed in spleen, liver and mesenteric lymph nodes after **oral administration**.

L46 ANSWER 8 OF 17 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1998205453 EMBASE Protective immunity induced by oral immunization with a rotavirus DNA **vaccine** encapsulated in microparticles. Chen S.C.; Jones D.H.; Fynan E.F.; Farrar G.H.; Clegg J.C.S.; Greenberg H.B.; Herrmann J.E.. J.E. Herrmann, Division of Infectious Diseases, Univ. of Massachusetts Med. School, 55 Lake Ave. North, Worcester, MA 01655, United States. John.E.Herrmann@banyan.ummed.edu. Journal of Virology 72/7 (5757-5761) 1998.
Refs: 38.
ISSN: 0022-538X. CODEN: JOVIAM. Pub. Country: United States. Language: English. Summary Language: English.

AB DNA **vaccines** are usually given by intramuscular injection or by gene gun delivery of DNA-coated particles into the epidermis. Induction of mucosal immunity by targeting DNA **vaccines** to mucosal surfaces may offer advantages, and an oral **vaccine** could be effective for controlling infections of the gut mucosa. In a murine model, we obtained protective immune responses after oral immunization with a rotavirus VP6 DNA **vaccine** encapsulated in poly(lactide- coglycolide) (PLG) microparticles. One dose of **vaccine** given to BALB/c mice elicited both rotavirus-specific serum antibodies and intestinal immunoglobulin A (IgA). After challenge at 12 weeks postimmunization with homologous rotavirus, fecal rotavirus antigen was significantly reduced compared with controls. Earlier and higher fecal rotavirus-specific IgA responses were noted during the peak period of viral shedding, suggesting that protection was due to specific mucosal immune responses. The results that we obtained with PLG-encapsulated rotavirus VP6 DNA are the first to demonstrate protection against an infectious agent elicited after **oral administration** of a DNA **vaccine**.

L46 ANSWER 9 OF 17 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1998125229 EMBASE Mucosal immunogenicity elicited in mice by oral **vaccination** with phosphorylcholine encapsulated in poly (D,L-lactide-co-glycolide) microspheres. Allaoui-Attarki K.; Fattal E.; Pecquet S.; Trolle S.; Chachaty E.; Couvreur P.; Andremont A.. A. Andremont, Laboratoire de Bacteriologie, Groupe Hosp. Bichat-Claude Bernard, 46 Rue Henri-Huchard, 75877 Paris Cedex 18, France. Vaccine 16/7 (685-691) 1998.
Refs: 47.
ISSN: 0264-410X. CODEN: VACCDE.
Publisher Ident.: S 0264-410X(97)00261-2. Pub. Country: United Kingdom.
Language: English. Summary Language: English.
AB Poly(D,L-lactide-co-glycolide) microspheres loaded with phosphorylcholine linked to thyroglobulin (PC-Thyr) as protein carrier were prepared. The entrapment efficiency reached 80% when the initial protein: polymer ratio was 1:8. Ninety-four percent of the loaded microspheres had a diameter .ltoreq. 10 .mu.m. The encapsulation process did not alter PC-Thyr absorbance nor PC antigenic reactivity. **Oral administration** of these microspheres induced a specific IgA response in intestinal, pulmonary and vaginal secretions, as well as a strong specific systemic immune response in female Balb/c mice. This suggests the need to explore further the potential ability of PC-Thyr loaded microspheres to protect against infections caused by PC-bearing microorganisms which invade or colonize different mucosal sites.

L46 ANSWER 10 OF 17 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1998244290 EMBASE Can **oral administration** of PLGA encapsulated fimbriae F18 elicit an immune response in pigs against edema disease and postweaning E. coli diarrhea?. Felder Ch.B.; Vorlaender N.; Merkle H.P.; Gander B.; Sydler T.; Bertschinger H.U.. Ch.B. Felder, Department of Pharmacy, University of Zurich, 8057 Zurich, Switzerland. Proceedings of the Controlled Release Society -/25 (631-632) 1998.
Refs: 3.
ISSN: 1022-0178. CODEN: 58GMAH. Pub. Country: United States. Language: English.

L46 ANSWER 11 OF 17 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1998398333 EMBASE The preparation and characterization of polymeric antigen delivery systems for **oral administration**. Singh M.; O'Hagan D.. M. Singh, Adjuvant Research Division, Chiron Corporation, 4560

Horton Street, Emeryville, CA 94608, United States. Advanced Drug Delivery
Reviews 34/2-3 (285-304) 1998.
Refs: 90.
ISSN: 0169-409X. CODEN: ADDREP.
Publisher Ident.: S 0169-409X(98)00044-1. Pub. Country: Netherlands.
Language: English. Summary Language: English.
AB Although polymeric delivery systems are well established for the **oral administration** of conventional drugs, they have not yet been commercially developed for **vaccine** delivery. The problems inherent with the oral route of delivery, including low pH, gastric enzymes, rapid transit and poor absorption of large molecules, has made the goal of oral delivery of antigens very challenging. Nevertheless, several polymeric delivery systems for the **oral administration** of **vaccines** are currently being evaluated, including microencapsulation in poly(lactide-co-glycolides), alginates, polyanhydrides, starch, polymethacrylates, polyamino acids and enteric coating polymers. These approaches are designed to protect the antigen in the gut, to target the antigen to the gut-associated lymphoid tissue, or to increase the residence time of the antigen in the gut through bioadhesion. Each of these approaches is discussed in relation to antigen encapsulation and integrity, process reproducibility, ease of preparation and encapsulation efficiency. Potential problems associated with the scale-up of these approaches are also briefly addressed. Of particular relevance are the prospects for the application of these formulation processes for commercial development. Copyright (C) 1998 Elsevier Science B.V.

L46 ANSWER 12 OF 17 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
97205274 EMBASE Document No.: 1997205274. Poly(DL-lactide-co-glycolide)-encapsulated plasmid DNA elicits systemic and mucosal antibody responses to encoded protein after **oral administration**. Jones D.H.; Corris S.; McDonald S.; Clegg J.C.S.; Farrar G.H.. J.C.S. Clegg, Applied Microbiology/Research Ctr., Porton Down, Salisbury, SP4 0JG, United Kingdom. Vaccine 15/8 (814-817) 1997.
Refs: 10.
ISSN: 0264-410X. CODEN: VACCDE.
Publisher Ident.: S 0264-410X(96)00266-6. Pub. Country: United Kingdom.
Language: English. Summary Language: English.
AB We have developed a method for the encapsulation of plasmid DNA in poly(DL-lactide-co-glycolide) microparticles. Encapsulated DNA, expressing the insect protein luciferase under the transcriptional control of the human cytomegalovirus immediate early promoter, was administered to mice by intraperitoneal injection or oral garage. Intraperitoneal injection of encapsulated DNA elicited good serum IgG and IgM responses, and a modest IgA response. **Oral administration** stimulated good serum antibody responses in all three classes, and in addition, significant levels of mucosal IgA. PLG encapsulation thus has the ability to protect plasmid DNA against degradation after administration, and to facilitate its uptake into appropriate cells for the subsequent expression and presentation of antigen, in such a way as to elicit both systemic and mucosal antibody responses. These findings may have major implications for the design of novel **vaccines** and delivery strategies.

L46 ANSWER 13 OF 17 CAPLUS COPYRIGHT 2000 ACS
1995:970076 Document No. 124:97349 Biodegradable microparticles as oral

vaccines. O'Hagan, D.T.; Jeffery, H.; Maloy, K.J.; Mowat, A. McI.; Rahman, D.; Challacombe, S.J. (Department of Pharmaceutical Sciences, University of Nottingham, Nottingham, NG7 2RD, UK). Adv. Exp. Med. Biol., Volume Date 1995, 371B, 1463-7 (English) 1995. CODEN: AEMBAP.
ISSN: 0065-2598.

AB Controlled-release microparticles have considerable potential both as parenteral and oral antigen delivery systems. Poly(lactide-co-glycolide) (PLG) microparticles induce both secretory and systemic antibody responses to entrapped ovalbumin (OVA) following **oral administration**. The **oral administration** of PLG microparticles results in the induction of OVA-specific cytotoxic T lymphocyte responses to entrapped OVA.

L46 ANSWER 14 OF 17 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

95275070 EMBASE Document No.: 1995275070. The preparation, characterization and pre-clinical evaluation of an orally administered HIV-1 **vaccine**, consisting of a branched peptide immunogen entrapped in controlled release microparticles. O'Hagan D.T.; McGee J.P.; Boyle R.; Gumaer D.; Li X.-M.; Potts B.; Wang C.Y.; Koff W.C.. United Biomedical Inc.,Hauppauge, NY 11788, United States. Journal of Controlled Release 36/1-2 (75-84) 1995.
ISSN: 0168-3659. CODEN: JCREEC. Pub. Country: Netherlands. Language: English. Summary Language: English.

AB A microencapsulated **vaccine** was prepared, containing a branched peptide immunogen (200M), representing a portion of the principal neutralizing determinant of HIV-1, entrapped in poly (lactide-co-glycolide) microparticles. Following extensive in vitro characterization of the microparticles, which included assessments of particle size and size distributions, microparticle surface structure, antigen loading level and efficiency of entrapment, moisture content, the levels of residual solvent, the in vitro release rate, an assessment of antigen integrity, the product bioburden and stability during storage, the microparticles were assessed in vivo. The initial assessments undertaken, involved studies in different animal species to determine the safety and pyrogenicity of the **vaccine** and also the toxicity following **oral administration**. Once the microparticles had been shown to be safe, pyrogen free and non-toxic, they were assessed for their ability to induce serum IgG and neutralizing antibody responses in guinea pigs. Following oral immunization alone, and combined oral and subcutaneous immunization, the microparticles were shown to induce high levels of both serum IgG and neutralizing antibodies against HIV. Pending review by the U.S. Food and Drugs Administration, the microparticle based oral **vaccine** against HIV-1 will be assessed in clinical trials in seronegative human volunteers.

L46 ANSWER 15 OF 17 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

94313643 EMBASE Document No.: 1994313643. Oral delivery of poly(lactide-co-glycoside) microspheres containing ovalbumin as **vaccine** formulation: Particle size study. Uchida T.; Goto S.. Faculty of Pharmaceutical Sciences, Kyushu University, Maidashi 3-1-1,Higashi-ku, Fukuoka 812, Japan. Biological and Pharmaceutical Bulletin 17/9 (1272-1276) 1994.
ISSN: 0918-6158. CODEN: BPBLEO. Pub. Country: Japan. Language: English. Summary Language: English.

AB The objective of the present study was to produce ovalbumin (OVA) loaded poly(lactide-co-glycolide) (PLGA) microspheres with different diameters and to evaluate their possibilities as **vaccine** formulation in

mice following oral inoculation. Four kinds of OVA loaded PLGA microspheres with different mean average volume diameters (1.3, 4.0, 7.5, and 14.0 .mu.m) were manufactured using a w/o/w emulsion/solvent evaporation method. Low loading efficiencies (8-20% w/w) were observed in all batches although smooth spherical particles were obtained. Single **oral administrations** of OVA loaded PLGA microspheres with different diameters to mice produced immune responses (serum IgG levels by ELISA) which were statistically higher than OVA solution as negative control (Fisher's paired t-test). A dose-response was observed, and single and double inoculation orally produced similar serum antibody levels. The rank of immune response was as follows: 4.0 .mu.m- > 1.3 .mu.m- = 7.5 .mu.m- > 14.0 .mu.m-microspheres. The oral inoculation with 0.13% OVA loaded PLGA microspheres having a mean volume diameter of 4.0 .mu.m exhibited the best immune responses with values greater than those obtained after subcutaneous inoculation with complete Freund's adjuvant (CFA) as positive control, and not significantly different from those obtained after subcutaneous inoculation with the same microspheres.

L46 ANSWER 16 OF 17 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
94226152 EMBASE Document No.: 1994226152. Dose and load studies for subcutaneous and oral delivery of poly(lactide- co-glycolide) microspheres containing ovalbumin. Uchida T.; Martin S.; Foster T.P.; Wardley R.C.; Grimm S.. Faculty of Pharmaceutical Sciences, Kyushu University, Maidashi 3-1-1,Higashi-ku, Fukuoka 812, Japan. Pharmaceutical Research 11/7 (1009-1015) 1994.
ISSN: 0724-8741. CODEN: PHREEB. Pub. Country: United States. Language: English. Summary Language: English.
AB Poly(lactide-co-glycolide) microspheres containing different loads of OVA (0.05, 0.1, 0.5 and 1.0% w/w) were manufactured by a w/o/w emulsion/solvent evaporation method. Low load efficiencies of less than 20% were observed. Normal size distributions with mean volume diameters ranging from 3.7 to 4.7 .mu.m were obtained for different batches. The in vitro release of OVA from different loaded microspheres showed an expected burst release with all batches. The in vivo dose study (1, 10, 25, 50 .mu.g of OVA) was performed by subcutaneous and oral inoculation in mice by single (0 week) or double (0 and 3 weeks) administration of PLGA 50/50 microspheres containing 0.1% OVA. Subcutaneous administration showed an immune response (serum Ig levels by ELISA) statistically (Fisher's paired t-test; $P < 0.05$) above OVA saline negative controls at 3, 6 and 12 weeks after administration. **Oral administration** of microspheres produced statistically higher systemic immune responses at the higher doses. Single and double inoculation orally and subcutaneously produced similar serum antibody levels. The in vivo load study was performed by subcutaneous and **oral administration** to mice of 25 .mu.g OVA contained in various loaded (0.05, 0.1, 0.5 and 1.0% w/w) microspheres. Serum immune responses at 3, 6, and 12 weeks after inoculation were statistically above OVA saline controls and were inversely proportional to the OVA load using either route. This observation suggested a relationship between the number of microspheres delivered and the in vivo serum response. Single subcutaneous administration of 0.05 or 0.1% OVA loaded PLGA 50/50 microspheres induced larger immune responses compared with complete Freund's adjuvant.

L46 ANSWER 17 OF 17 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1993-078590 [10] WPIDS
AB EP 531091 A UPAB: 19931122
Biodegradable copolyesters (I) comprising units of formula (II) and (III) are new. In the formulae, X = H or COR; R = 1-20C hydrocarbyl or 1-20C alkoxy (but see below); Y = H or 1-8C alkyl; m and n = 1 or more, provided

that m+n = 10 or more and m/(m+n) = 0.01 or more.
Pref. R = 1-20C alkyl, 4-8C alkoxy or 7-9C aralkoxy; Y = H or Me. Pref. (I) may be prepd. by copolymerising the corresp. hydroxy acids.
USE/ADVANTAGE - (I) are useful as carriers for controlled release of drugs (esp. peptides or proteins), antibodies or **vaccines**. They are suitable for parenteral, oral or nasal admin. and eliminate the `initial burst' phenomenon associated with glycolide-lactide **copolymers**.
In an example, a mixt. of 3.2g trans-4-hydroxy-L-proline, 20g DL-**lactic acid** and 0.4g HCl-activated `Dowex 50W' was heated at 130-140 deg. C and 15mm Hg for 2-3 hr., heated at 175 deg. C and 1mm Hg for 60 hr., dissolved in CH2Cl2, filtered, and diluted with hexane to ppte. the **copolymer** (5g, m.pt. 45 deg. C). The prod. had a Mw of 4000 and a hydroxyproline:**lactic acid** ratio of 30:70.
0/0
.
Dwg.0/0

ABEQ JP 05202177 A UPAB: 19931122
Copolymer has structural units of formula (I) and (II). In formulae, X is H, or COR; R = 1-20C hydrocarbon or alkoxy; Y = H, 1-8C alkyl; m, n are each at least 1, and m + n is at least 10; m/(m + n) is at least 0.01.
Pref. R = 1-20C alkyl, 4-8C aliphatic alkoxy or 7-9C aromatic alkoxy (sic); Y = H or methyl.
Medical compsn. comprises a **copolymer** of trans-4-hydroxy-L-proline and **lactic acid** and/or **glycolic acid**, mixed with a medicine. pref. as a moulded particulate of average dia. 0.01-400 micron, esp. a **vaccine**.
USE/ADVANTAGE - Used in a hypodermic injection and intramuscular injection. Also in a **vaccine** for **oral administration**. Product is biodegradable and excels in slow release of medicines.
Dwg.0/1

ABEQ US 5395916 A UPAB: 19950425
Biodegradable trans-4-hydroxy-L-proline opt. N-substd. **copolymer** having structural units of formula (I) and (II) is new. In the formula, X is H, acyl of formula RCO, where R is 1-20C hydrocarbons or 1-20C alkoxy; Y is H, 1-8C alkyl; m and n are each at least with m+n at least 10 and m(m+n) at least 0.01.
USE - Drug delivery systems for controlling drug kinetics, esp. by suppressing initial burst.
Dwg.0/1

ABEQ EP 531091 B UPAB: 19950824
A biodegradable **copolymer** having the constituent units represented by the structures (I) and (II) wherein X represents a hydrogen atom, an acyl group having the formula RCO - where R is a hydrocarbon group having 1 to 20 carbon atoms, an alkoxy group having 1 to 20 carbon atoms, and Y represents a hydrogen atom or an alkyl group having 1 to 8 carbon atoms, and m and n are independently integers of 1 or more, m + n is at least 10 and m/(m + n) is at least 0.01.
Dwg.0/1

=> del his y

=> fil reg